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Chemotherapy of Disseminated Testicular Cancer

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Dramatic improvements have been made in recent years in treatment of disseminated testicular cancer. Germ-cell neoplasms, even when advanced, are potentially curable by modern chemotherapy. Although disseminated testicular cancer is a rare disease, it is highly treatable, and primary physicians, internists and urologists should have some knowledge of its management.

IN THE 1960's dactinomycin alone or in combination with other drugs was the standard chemotherapy for testicular cancer. Complete disappearance of the disease occurred in about 15 percent of patients who received such treatment. Relapse would occur in about half of these patients, but the others would be cured.[1] Therefore, while the complete remission rate was relatively low with this therapy, the durability of remission was reasonably good.

In the late 1960's and early 1970's several new drugs effective in treating testicular cancer were introduced—vinblastine sulfate (Velban), bleomycin sulfate and mithramycin. These drugs, when used alone, have essentially the same degree of activity as dactinomycin. Of particular interest were vinblastine and bleomycin. The major toxic effect of vinblastine is myelosuppression, and that of bleomycin is pulmonary fibrosis. These drugs can be given in full dosage when used together. In addition, by virtue of their mechanisms of action, they appear to be synergistic. Results of studies at the University of Texas M. D. Anderson Hospital and Tumor Institute at Houston have shown that this regimen will produce complete responses in approximately 45 percent of patients.[2] Relapse occurred in only 33 percent, and many of these patients presumably are cured.

The newest active drug used to treat testicular cancer is Cis-diamminedichloroplatinum (DDP). It is probably the single most active agent. It is fairly toxic and the most notable problems are vomiting and nephrotoxicity; it almost never results in myelosuppression and, therefore, will combine well with vinblastine and bleomycin.

From August 1974 to September 1976, a total of 50 patients with disseminated testicular cancer were treated with DDP, vinblastine and bleomycin at Indiana University.[3] Table 1 outlines the treatment regimen. In 33 of 47 cases that could be evaluated, there was drug-induced disappearance of all disease. In five cases resection of residual tumor was done after almost total regression from chemotherapy. Recent analysis of these data shows that 33 of these patients are alive and 27 are without disease after from 21 to more than 45 months. Because most relapses of testicular cancer will occur within the first year, and practically all within two years, most if not all of these patients can be considered cured. These results are the best reported. Consequently we feel that optimal therapy for patients with metastatic testicular cancer is platinum-based combination chemotherapy.

Since September 1976 we have been evaluating the effects of lower dosages of vinblastine in an

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TABLE 1.—*Treatment Regimen Used In 50 Patients at Indiana University, August 1974 to September 1976*

Remission Induction
• Cis-diamminedichloroplatinum (DDP), 20 mg per square meter given intravenously every day for five days
• Vinblastine sulfate (Velban), 0.2 mg per kg of body weight given in an intravenous push on days one and two of each course
• Bleomycin sulfate, 30 units given in an intravenous push six hours after Vinblastine on day two of each course and once a week for 12 weeks
Given every three weeks for three to four courses with continuous intravenous hydration
Maintenance
Vinblastine, 0.3 mg per kg of body weight, given every four weeks for a total of two years of therapy

attempt to reduce toxicity without lowering therapeutic efficacy. At present, it appears that equivalent results can be achieved by using a 25 percent reduction in dose (0.3 mg per kg of body weight) of vinblastine during remission induction.

Specific Aspects of Management

Markers

There is no other malignant condition in which tumor markers are as important as in testicular cancer. Most useful are assays of B-subunit chorionic gonadotropin (B-HCG) and α-fetoprotein (AFP). When measured by sensitive radioimmunoassay, elevations of one or both of these markers will occur in 90 percent of patients with active tumors. There are essentially no false positive findings and a patient with a history of testicular cancer who has an elevated marker must be considered to have an active tumor even if results of all other studies are normal and should be given appropriate treatment.[4] Moreover, in a patient with metastatic disease, the level of marker correlates well with the response to therapy, and markers must return to a normal level before the patient can be considered free from disease. It cannot be emphasized too strongly, however, that these tests must be done on serum by radioimmunoassay because other techniques are much too insensitive.

Side Effects of Chemotherapy

Aggressive combination chemotherapy for disseminated testicular cancer can be quite toxic, and such patients are best managed by trained medical oncologists. Alopecia, nausea, vomiting, paresthesias and constipation are troublesome but reversible side effects. Of major concern is myelosuppression, which is universal, particularly in patients who have had previous therapy with radiation. Consequently, if granulocytopenic fever develops, patients must be promptly admitted to hospital; cultures must be done, and broad-spectrum antibiotics—usually cephalosporin and carbenicillin—must be administered. Use of aminoglycoside antibiotics should be avoided because it may produce synergistic nephrotoxicity with DDP. DDP is potentially nephrotoxic and a variety of maneuvers have been used to ameliorate renal damage. In our experience, vigorous hydration with normal saline solution is sufficient. Physicians must be willing to carry out aggressive treatment and must be equipped to deal with toxicity because, ultimately, cure of these patients depends on such an approach.

Follow-up Examination

A major determinant of the prognosis in a particular case is the extent of disease at the time chemotherapy is begun. In patients with minimal metastatic disease there is a high probability (19 of 22 in our series) of complete remission occurring; consequently, careful follow-up examinations of all patients with testicular cancer is crucial. We obtain x-rays of the chest and assays of B-HCG and AFP every month for the first year in every patient, and every other month for the second year after surgical operation for localized disease or chemotherapy for disseminated disease. Therefore, recurrent disease can be diagnosed early, at a time when chemotherapy is most likely curative.

Integrated Management of Local Disease

Most patients with testicular cancer present initially with disease localized to the testis or to testis and retroperitoneal nodes. Diagnosis is confirmed on inguinal orchiectomy. Patients with pure seminoma ordinarily are treated with radiotherapy and there is an extremely high probability of cure. However, the approach in cases of nonseminomatous neoplasms (embryonal, teratoma or choriocarcinoma, or mixtures) is considerably different. If there is disease present outside the testis and draining lymphatics (usually shown as pulmonary metastatic lesions) the first approach should be platinum-based combination chemotherapy.

However, if results of thorough examination, including tomograms of the whole lung, show no

supradiaphragmatic disease, we favor proceeding with radical bilateral retroperitoneal lymph node dissection. If the nodes are normal, therapy is completed and there is a high probability of cure. As mentioned previously, however, careful follow-up examination, with x-ray studies of the chest and assays of B-HCG and AFP, is required.

There is considerably more controversy about proper management of abnormal retroperitoneal nodes. Many clinicians use preoperative or postoperative radiation therapy, or both, in this situation.[5,6] However, urologists who use surgical therapy alone seem to have equivalent results.[7,8] Whatever form of therapy is used, in about half of the patients relapse will occur and systemic therapy will be required. In our experience, there has been poor tolerance of chemotherapy and a lower rate of complete remission in patients in whom irradiation has been done. We do not use radiotherapy, therefore, in these cases.

We are frequently asked our opinion of the role of adjuvant chemotherapy in patients in whom findings are positive on resection of retroperitoneal nodes. A number of these patients are cured by surgical operation alone. Of the patients in whom relapse occurs, a sizable number will be cured by chemotherapy, particularly if the relapse is diagnosed early. Consequently, the usefulness of adjuvant therapy is open to question and answers can only be determined by a well-designed, controlled clinical trial. Such a study is now in progress.

Conclusions

Disseminated testicular cancer is a highly treatable disease and approximately half of all patients can be cured with chemotherapy. The treatment is vigorous and requires the services of experienced physicians. In all phases of the disease regular follow-up examinations consisting of x-rays of the chest and tumor marker studies should be done. Chemotherapy may be useful as adjuvant treatment, but a controlled clinical trial is required to define its usefulness.

REFERENCES

1. Ansfield FJ, Korbitz BC, Davis HC, et al: Triple drug therapy in testicular tumors. Cancer 24:442-446, 1969

2. Samuels ML, Lanzotti VJ, Holoye PY, et al: Combination chemotherapy in germinal cell tumors. Cancer Treat Rep 3:185-204, 1976

3. Einhorn LH, Donohue JP: Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Intern Med 87:293-298, 1977

4. Lange PH, Fraley EE: Serum alpha-fetoprotein and human chorionic gonadotropin in the treatment of patients with testicular tumors. Urol Clin North Am 4:393-406, 1977

5. Tyrell CJ, Peckham MJ: The response of lymph node metastases of testicular teratoma to radiation therapy. Br J Urol 48: 363-370, 1976

6. Maier JG, Mittemeyer B: Carcinoma of the testis. Cancer 39:981-986, 1977

7. Donohue JP: Retroperitoneal lymphadenectomy. Urol Clin North Am 4:509-521, 1977

8. Staubitz WJ, Early KS, Magoss IV, et al: Surgical management of testis tumor. Urology 111:205-209, 1974